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INVERSINE

The prognosis in malignant or accelerated hypertension, almost uniformly fatal within a year if left untreated, has been much improved by the use of antihypertensive drugs. In moderately severe and severe hypertension which has not yet entered the malignant phase, reduction of blood pressure often results in better control of congestive heart failure and retinopathy, fewer strokes, slower progression of renal failure and relief of headache and other symptoms.

Mecamylamine hydrochloride (Inversine-Merck) is one of a group of potent and useful ganglionic blocking agents for the treatment of severe and malignant hypertension. Others are hexamethonium (Bistrium-Squibb; and other brands), pentolinium (Ansolysen-Wyeth), and chlorisondamine (Ecolid-Ciba). Inversine is available only in oral form, and it is almost completely absorbed from the gastrointestinal tract; when other blocking agents are taken orally, their absorption and their hypotensive effects are influenced by fluctuations in gastrointestinal activity. The effects of Inversine differ markedly in different patients, requiring careful regulation of each patient, but they are fairly constant in the same patient. This uniformity of action is an important advantage, but it is obtained at the expense of the drug's more severe central nervous system side effects, and its greater tendency to cause constipation. Like all potent blocking agents, Inversine must be used with great caution to avoid severe hypotensive episodes.

DOSAGE - The recommended starting dose is 2.5 mg. twice a day after meals. If greater antihypertensive effect is required, dosage is increased to 5 mg. twice daily for the second week and, if needed, 5 mg. four times a day beginning with the third week. Blood pressure should always be determined with the patient standing, since the hypotensive effects of such drugs are maximal in this position. Since therapeutically effective doses always carry the risk of serious hypotensive episodes, the patient should report promptly any attacks of dizziness or weakness. Some physicians have the patient do blood pressure determinations at home to help regulate dosage. Dosage requirements, in general, will be less after sympathectomy and under conditions of sodium depletion induced by diuretics. Combined therapy with chlorothiazide or with hypotensive drugs requires reduction in the doses of Inversine or other ganglionic blockers by about 50 per cent. In patients receiving other antihypertension medication, the initial dose of Inversine should be lower than that noted above.

SIDE EFFECTS - Side effects are for the most part of the same types as those seen with other ganglionic blocking agents. Postural hypotension, blurred vision, dry mouth, and constipation are the most frequent; paralytic ileus must especially be guarded against. Such drugs as cascara and neostigmine (15 to 30 mg. before meals) are helpful in treatment of constipation and prevention of ileus. Pilocarpine (5 to 10 mg. before meals) may help relieve dry mouth. The urinary retention, paresthesias, coarse tremor, mental confusion, and other central nervous system side effects of Inversine are generally reversible, but some clinicians feel that they limit the usefulness of the drug. Postural hypotension carries with it the risk of myocardial infarction with or without thrombosis, making careful regulation of dosage essential. Severe hypotensive episodes should, of course, be combated with such drugs as Levophed, Neosynephrine, Aramine and Vasoxyl.

Inversine and other ganglionic blockers should be used with extreme caution in patients with azotemia, since glomerular filtration is decreased by the drug when there is a significant fall in blood pressure. Like all ganglionic blocking agents, it is contraindicated in patients with recent myocardial infarction or cerebral thrombosis, coronary insufficiency, glaucoma, and organic pyloric stenosis. Because of its potent action and side effects, Inversine should be reserved for patients with severe and malignant hypertension who do not respond to less potent drugs.

CLARIN

A very small dose of intravenous heparin reduces the neutral-fat (though not the cholesterol) content of blood plasma, and there is evidence that heparin in the form of sublingual tablets has a similar effect on the hyperlipemia which occurs after a fatty meal. Furthermore, elevated neutral-fat levels have been found in the serum of patients with coronary artery disease. On the basis of this evidence, Clarin (Leeming) heparin tablets are offered with the claim that "one mint-flavored Clarin tablet under the tongue after each meal regularly controls hyperlipemia," and is an "aid to the management of atherosclerosis."

Hyperlipemia following ingestion of a lipid emulsion (as measured by optical density of serum) has been reduced significantly by a single 1500-unit sublingual tablet of heparin (H. L. Fuller, Angiology, 9: 311, 1958; H. E. Shaftel and D. Selman, Angiology, 10: 131, June, 1959). A preliminary report on a small series of subjects given a test meal of I_{131}-labeled triolein in peanut oil showed a favorable effect with two tablets of Clarin taken sublingually immediately after the meal and again three hours and five hours later (D. Berkowitz, et al., Clinical Research, 7: 255, 1959). Effectiveness was determined by measurement of serum radioactivity, triglycerides, unesterified fatty acids, and optical density.

An effort to demonstrate lipolytic activity in vitro in the plasma of subjects given Clarin was unsuccessful (H. Engelberg, JAMA, 169: 1322, 1959), possibly because the techniques used were not sufficiently sensitive. Only a small percentage of heparin which is taken sublingually is absorbed, certainly not enough to influence clotting, but apparently enough to affect the rise in blood fats after

ingestion of fat emulsions. Further experience with size, timing and frequency of dose may show that proper dosage can materially reduce postprandial hyperlipemia under usual dietary conditions. Despite such physiologic effects, however, carefully controlled, long-term clinical studies will be necessary to determine whether such reduction will alter the course of atherosclerosis. At this point, the use of Clarin in the management of hyperlipemia and atherosclerosis must be considered experimental. Each Clarin tablet contains 1500 units of heparin potassium, and costs the patient about 20¢ in quantities of 50 or more.

ORAL IRON PREPARATIONS

Some 250 products containing iron are listed in pharmaceutical directories, and hardly a month goes by without the announcement of new ones. Their great number and variety, and the frequent claim that this or that preparation is better absorbed, or less irritating to the gastrointestinal tract than others, add a good deal of confusion to what is essentially a simple situation. The effectiveness of an iron preparation is determined solely by the amount of elemental iron absorbed, and except in terms of the amount absorbed, effectiveness has nothing to do with the original chemical form. Once absorbed, the iron is combined with a specific protein to produce transferrin, and the original form of the iron in no way affects the utilization of transferrin.

In relation to the iron contained in the preparation, there is normally no appreciable difference in the amount of iron absorbed from the commonly used iron compounds such as ferrous sulfate, ferrous gluconate, ferrous carbonate and ferric ammonium citrate. Since ferric iron must be reduced to the ferrous form before absorption, however, and gastrointestinal conditions may, in a few patients, interfere with reduction, a ferrous salt should be selected.

SPECIAL FORMS - Although chelated iron compounds have been heavily promoted, not enough work has been done to establish whether there is better or poorer absorption than with ferrous sulfate. Nor is there convincing evidence that copper, molybdenum, liver extract, or any of the B vitamins enhance the absorption of iron in iron-deficient patients. Experimental studies indicate that ascorbic acid may enhance the absorption of iron somewhat, but at best the effect is too slight to justify the inclusion of this vitamin in iron preparations. Cobalt salts have also been promoted as adjuncts to iron, but proof is lacking that they increase either absorption or utilization of iron. Long-term administration of cobaltous chloride has occasionally had goitrogenic and thyroid-depressing effects in children (R. J. Gross, et al., Pediatrics, 15:284, 1955).

Whatever the preparation used, within limits, the amount of iron absorbed increases with the amount administered; and the amount administered is limited by the gastric irritation caused by the iron. It has never been demonstrated convincingly that gastric irritation is influenced by anything except the amount of ionic iron present after it has been split off from the molecule containing it. The claim that certain preparations are less irritating than others is usually valid only to the extent that they contain smaller amounts of ionizable iron. Equivalent doses of a simple ferrous salt would be tolerated just as well.

IRON CONTENT AND COST - The difference in iron content of different preparations is not always appreciated. That is why ferrous gluconate is sometimes thought to be less irritating than ferrous sulfate. Comparison of the amounts of iron in equal doses shows why ferrous gluconate is "less irritating":

Form	Iron per gram
Exsiccated ferrous sulfate ($FeSO_4 \cdot H_2O$)	330 mg.
Ferrous sulfate ($FeSO_4 \cdot 7H_2O$)	200 mg.
Ferrous gluconate	115 mg.

Although iron salts are better absorbed when they are taken between meals, they may be taken with or immediately after meals to minimize gastrointestinal irritation and diarrhea. For the same reason it is desirable to start iron therapy with small doses and to increase the dose gradually. There is no evidence that gastric acidity (or giving hydrochloric acid to patients with low gastric acidity) significantly affects the absorption of ferrous iron.

In general, special forms of iron or mixtures of iron with accessory factors are relatively expensive in terms of iron content, as shown by the following table:

Preparation	Content	Iron per tablet	Approximate cost per tablet	Approximate cost/100 mg. iron
Exs. Ferrous Sulfate USP	195 mg. exs. ferrous sulfate	65 mg.	1¢	1.5¢
Feosol Tablets (SKF)	195 mg. exs. ferrous sulfate	65 mg.	1.5¢	2.3¢
Feosol Spansules (SKF)	150 mg. exs. ferrous sulfate	50 mg.	9¢	18¢
Fergon (Winthrop)	325 mg. ferrous gluconate	40 mg.	1.5¢	3.8¢
Chel-Iron (Kinney)	330 mg. iron choline citrate	40 mg.	3¢	7.5¢
Mol-Iron (White)	195 mg. ferrous sulfate (plus molybdenum oxide)	40 mg.	1.5¢	3.8¢
Roncovite (Lloyd)	200 mg. exs. ferrous sulfate (plus cobalt chloride)	67 mg.	4.5¢	6.8¢

Iron preparations should be kept where they will be out of the reach of small children. Accidental ingestion of large amounts of iron can produce serious and even fatal toxicity (N. J. Smith, J. of Pediatrics, 53: 37, 1958).

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